

Which denoising for resting-state based parcellation?: reliability & reproducibility in hippocampus

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Connectivity-Based Parcellation (CBP) identifies distinct subregions by clustering voxels based on their connectivity fingerprint [1]. In that context, resting-state functional connectivity (RSFC), meta-analytic connectivity modeling (MACM), and structural covariance (SC) provide complementary windows into regional differentiation. Due to its relatively high accessibility, RSFC-CBP has been most widely used to examine brain organization. While several denoising strategies can be used in that purpose, their effects on CBP has not yet been investigated. Here, we examined the reliability and reproducibility of RSFC-CBP as a function of different denoising approaches in one of the most studied brain regions, the hippocampus.

Our VOI was defined based on micro- and macro-structure [2,3,4]. Group-level parcellations (RSFC-CBP and SC-CBP) were performed on functional and structural MRI data of two cohorts: 1000BRAINS (n = 671) and HCP (n = 323) [5,6]. RSFC was either 1) not denoised, or subjected to one of five common denoising strategies: 2) global signal regression (GSR) 3) white matter and CSF signal regression (WM/CSF) 4) FMRIB's ICA-based X-noisifier (FIX), 5) combinations of FIX and GSR, 6) FIX and WM/CSF regression. For cross-modal comparison SC-CBP was applied on grey matter probabilities modulated for non-linear transformations. MACM-CBP was performed based on co-activation profiles calculated across BrainMap studies [7].

In all cases, parcellation was performed by k-means for k=2-7. RSFC-CBP reliability was assessed with split-half cross-validation and RSFC-CBP reproducibility across cohorts and modalities (RSFC vs. MACM, SC) was evaluated by bootstrap resampling using the adjusted Rand Index (aRI) as a measure of partitions congruency. The influence of

denoising on the reliability and reproducibility of RSFC-CBP as well as on connectivity and dissimilarity of voxels was quantified using ANOVAs.

RSFC-CBP demonstrated high reliability across all denoising techniques (.79-.84 aRI) but GSR, WM/CSF and FIX+WM/CSF were the most reliable ($p < .0001$, Fig. 1A). The highest reproducibility of clusterings across samples (.52 aRI) and modalities ($< .45$ aRI) was likewise achieved with FIX+WM/CSF ($p < .0001$). Thus, we not only revealed a clear effect of denoising strategies but also converging evidence for FIX+WM/CSF as an optimal method for RS data cleaning (Fig. 1A). Upon further investigation of the driving mechanisms for this superiority, we found that FIX+GSR and FIX+WM/CSF significantly reduced the similarity between the time-courses of the seed voxels ($p < .0001$), and additionally enhanced the dissimilarity of their connectivity profiles ($p < .0001$) (Fig. 1B,C).

With FIX-WM/CSF the 2-cluster solution demonstrated the highest convergence across samples and between RSFC and SC ($p < .0001$) dividing the hippocampus into an anterior and posterior region (Fig. 2). The highest consistency between RSFC and MACM was observed for a 5-cluster solution ($p < .0001$) featuring a differentiation into tail, body and a three-way subdivision of the hippocampus head into a ventral, dorsolateral, and dorsomedial part (Fig. 2).

RSFC-CBP reliability and reproducibility

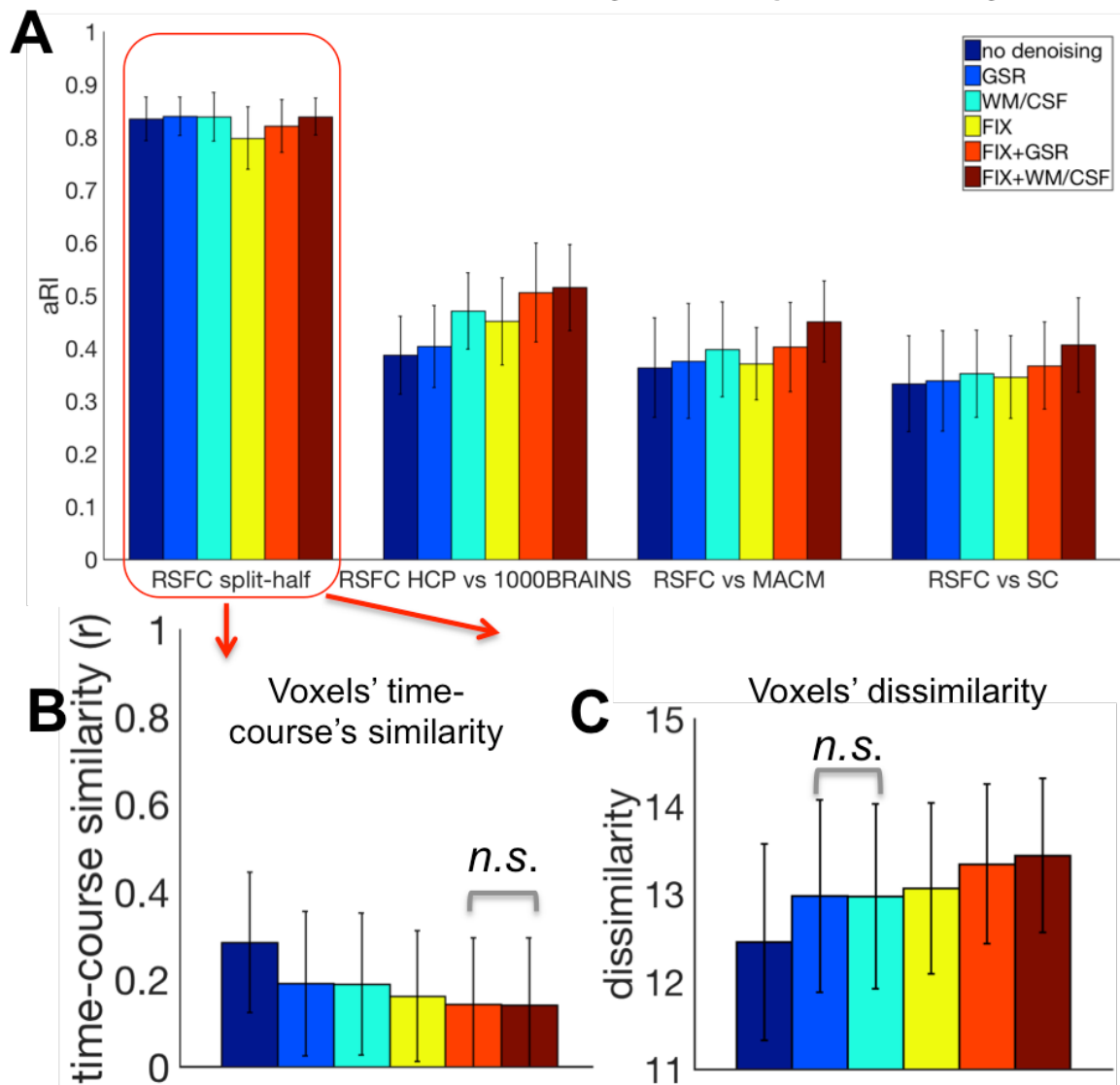


Figure 1. Note: bars represent mean and standard deviation.

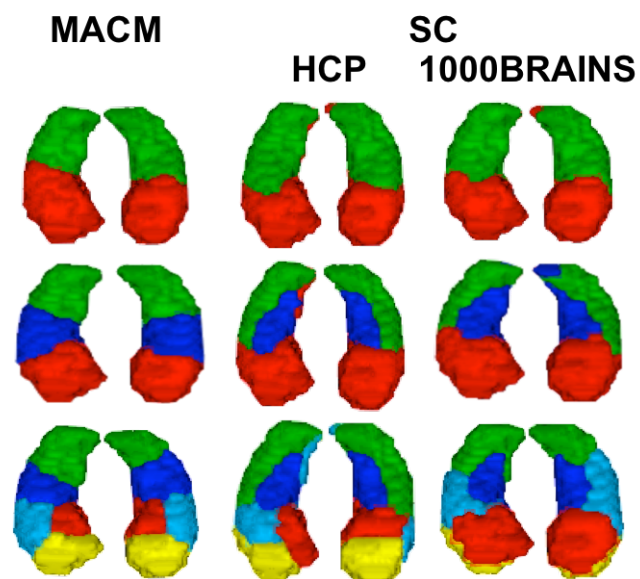
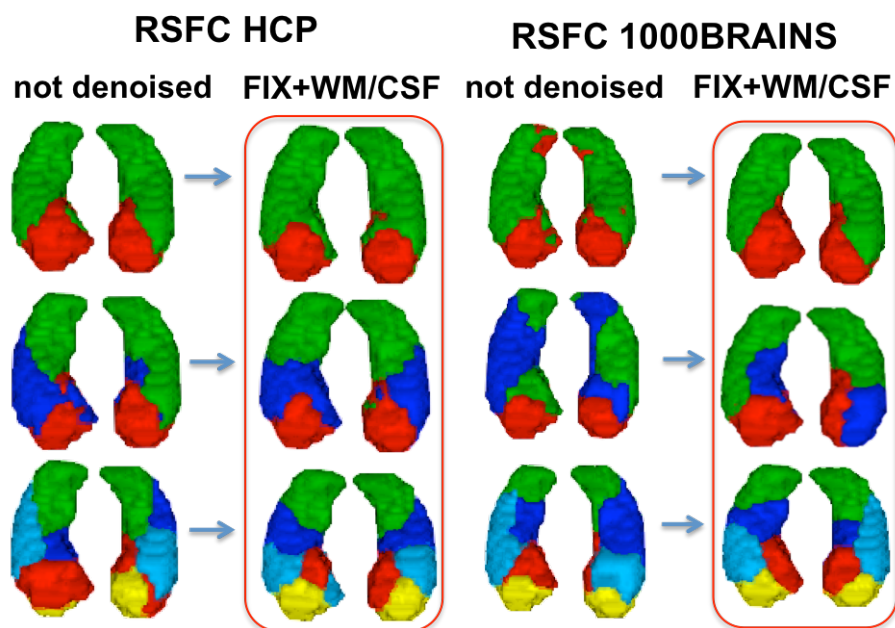
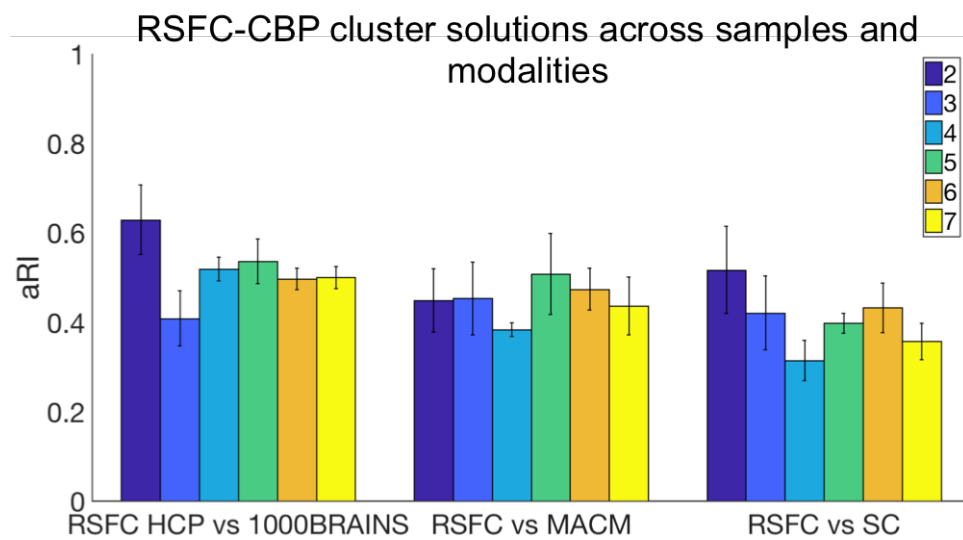


Figure 2. Note: bars represent mean and standard deviation.

The combination of a model-based and a model-free denoising strategy, FIX+WM/CSF, leads to stable clustering of the hippocampus. In particular, this approach successfully eliminated structured noise rendering the seed time-series' less inter-correlated and enhanced the distinctiveness of the connectivity profiles. Accordingly, FIX+WM/CSF also yielded most reproducible clusterings across samples and modalities. Overall, these results suggest a higher biological validity of RSFC-CBP after FIX+WM/CSF denoising, revealing a hippocampal organization confirmed by tracing, lesion and genetic studies across species [8,9,10]. Our study therefore proposes to promote FIX+WM/CSF as an optimal denoising strategy for RSFC-CBP and the examination of convergence from samples and modalities to determine optimal clustering solutions.

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